

I. STUDIES IN THE SYNTHESIS OF
p-NITROBENZENESULFONYL CHLORIDE

II. SYNTHESIS OF SOME QUINOLINE DERIVATIVES
WITH SULFUR-CONTAINING SUBSTITUENTS

III. SYNTHESIS OF 4-HYDROXYQUINOLINE DERIVATIVES
FROM AROMATIC AMINES AND OXALOACETIC ESTER

BY
GARDNER WESLEY STACY

B. S., University of Rochester, 1943

AN ABSTRACT OF A THESIS

SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS
FOR THE DEGREE OF DOCTOR OF PHILOSOPHY IN CHEMISTRY
IN THE GRADUATE SCHOOL OF THE
UNIVERSITY OF ILLINOIS, 1946

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PART ONE

STUDIES IN THE SYNTHESIS OF *p*-NITRO-BENZENESULFONYL CHLORIDE

INTRODUCTION

Certain sulfa drugs, such as sulfadiazine, sulfamerazine, and sulfamethazine, have been shown to possess activity against avian malaria. The preparation of these compounds has involved the use of *p*-nitrobenzenesulfonyl chloride which, however, has not been too readily available. The purpose of this research has been to investigate various methods for the preparation of this material.

DISCUSSION OF RESULTS

The procedure most used for the synthesis of *p*-nitrobenzenesulfonyl chloride has required as an intermediate *p*-nitrophenyl disulfide, prepared by the interaction of *p*-chloronitrobenzene and an ethanolic solution of sodium disulfide (1). In this reaction a considerable amount of by-product was obtained. This was assumed to be a dimorphic form of the disulfide by Hodgson and Wilson (2) and Elgersma (3) or an isomeric form by Vorozhtzov and Kozlov (4). On the other hand, Witte (5) and Bennett and Youle (6) considered the by-product to be the monosulfide.

To ascertain whether monosulfide was present as an impurity a melting-point diagram of the system monosulfide-disulfide was constructed. The low-melting by-product, described by many investigators, and thought to be a thio-sulfoxide by Vorozhtzov and Kozlov (4), was shown to have the same composition as the eutectic which correspond to a molecular compound containing two equivalents of monosulfide to one of disulfide.

In an attempt to depress the tendency toward monosulfide formation various amounts of sulfur in excess were used in the preparation of sodium disulfide. However, there

was no decrease in monosulfide formation with increase in sulfur concentration.

Since the synthesis of *p*-nitrobenzenesulfonyl chloride by way of *p*-nitrophenyl disulfide could not be improved because of the simultaneous formation of monosulfide, it was decided to utilize *p*-nitrothiophenol as an intermediate. Thiophenols have been obtained by alkaline hydrolysis of S-aryl xanthates which are prepared from the corresponding diazonium salts and potassium xanthate. It was thought in the present case, however, that the xanthate might be obtained directly by interaction of *p*-chloronitrobenzene and potassium xanthate because of the activated nature of the chlorine atom on the benzene ring. However, the xanthate was not obtained but instead, *p*-nitrophenyl sulfide in excellent yield. This seemed to be noteworthy because no satisfactory method of preparation for this sulfide has been described in the literature.

p-Nitrothiophenol was finally prepared by a modification of a method described by Brand (7), wherein *p*-chloronitrobenzene was allowed to react with an excess of alkaline sodium disulfide. This could then be converted directly to the sulfonyl chloride by oxidation with chlorine in a water-glacial acetic acid medium.

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PART TWO

SYNTHESIS OF SOME QUINOLINE DERIVATIVES WITH SULFUR-CONTAINING SUBSTITUENTS

INTRODUCTION

Sulfonamides and sulfones have been considered a potential source for therapeutic agents to combat malaria. For example, sulfadiazine, sulfamerazine, and sulfamethazine and derivatives of *p*-aminophenyl sulfone (1) have been found to be active against avian malaria, both as suppressives and prophylactics.

It, therefore, seemed of interest to attempt to combine the properties of sulfonamides and sulfones with those of therapeutically active quinoline derivatives. Since recent advances (2) have made 4-aminoquinoline derivatives more readily available, synthesis of derivatives of this series, substituted with a variety of sulfur-containing groups in the 6-position of the quinoline nucleus, was conceived.

DISCUSSION OF RESULTS

Initial efforts in this research were directed toward the synthesis of 4-chloro-6-quinolinesulfonamide, which was to be condensed with the desired basic side-chains. The most direct means of obtaining this compound appeared to be through the condensation of sulfanilamide with ethoxymethylenemalonic ester to form an anilinoacrylate, followed by thermal cyclization, removal of the ester group by hydrolysis, decarboxylation and replacement of the hydroxyl group by chlorine. Unfortunately, however, when attempts were made to cyclize the acrylate, only tarry products were obtained.

Still another approach was available, however, and that was to employ *p*-aminophenyl disulfide in the same type of synthesis. To obtain the desired product it was planned to convert 6,6'-bis-(4-hydroxyquinolyl) disulfide to the sulfonic acid and thence to the sulfonamide. 6,6'-Bis-(4-hydroxyquinolyl) disulfide could not be obtained, however, for the series of reactions described failed at the point of decarboxylation.

Because of the continued failure in the disulfide series full attention was turned to the corresponding sulfide series.

Here the reactions proceeded smoothly, although some interesting redox reactions involving the sulfur atom were encountered. For example, replacement of the hydroxyl group by chlorine in 6,6'-bis-(4-hydroxyquinolyl) sulfide was accompanied by the oxidation of the sulfur atom leading to the corresponding sulfoxide. On the other hand, heating 6,6'-bis-(4-chloroquinolyl) sulfoxide with Noval diamine in the presence of phenol at 210° apparently reduced the sulfoxide to the sulfide, aside from introducing the basic side-chain, to yield 6,6'-bis-(4-diethylamino-1-methylbutyl-aminoquinolyl) sulfide.

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PART THREE*

SYNTHESIS OF 4-HYDROXYQUINOLINE DERIVATIVES FROM AROMATIC AMINES AND OXALOACETIC ESTER

INTRODUCTION

4-Hydroxyquinolines are important intermediates in the preparation of certain 4-dialkylaminoalkylaminoquinoline derivatives, which have been shown to be excellent anti-parasitic agents. Because of this, attempts to find new methods of synthesizing 4-hydroxyquinolines and to improve existing methods have been the subject of extensive investigation. Such syntheses have been of significance in the light of industrial application to the large-scale production of a suitable antimalarial drug and because of the necessity of preparing a variety of derivatives for studies of correlation of structure and activity.

*A part of these investigations was carried out in the laboratories of the National Aniline Division, Allied Chemical and Dye Corporation. The helpful suggestions and assistance of George F. Lisk are herewith gratefully acknowledged.

Production of 7-chloro-4-hydroxyquinoline from sodio ethyl oxaloacetate and *m*-chloroaniline has not been satisfactory because of the isomeric 5-chloro derivative which is formed in equal amount. Yet, because of the attractive economic implications of this synthesis, it has been deemed expedient to investigate further the conditions under which cyclization of ethyl β -carbethoxy- β -(*m*-chloroanilino)acrylate might be accomplished.

DISCUSSION OF RESULTS

A study was made of the variation in the ratio of isomeric quinolines with the amount of diluent employed in cyclization. It was found that when limited amounts of diphenyl ether were used virtually all 5-isomer was obtained, while in the case of large amounts (30:1) about forty per cent 5-isomer resulted. However, at the same time the yield of combined dichloroquinolines varied from 17 per cent at two parts of diluent to one of acrylate to 28 per cent at 30:1, reaching a maximum of 32 per cent at 15:1.

Also an investigation of the importance of temperature in the cyclization was carried out, and it was found that much lower yields of cyclized product were obtained at lower temperatures, even after longer periods of heating. The ratio of isomers was in no way changed.

Since the ratio of isomers could not be altered favorably by modifying conditions of cyclization, another approach to the problem was initiated. The opportunity for the formation of a 5-isomer could be completely eliminated by use of a blocking group. Accordingly, 4,7-dichloro-8-methylquinoline was prepared by applying the synthesis to 6-chloro-*o*-toluidine. The chloro derivative was condensed with 4-amino-1-ethylpiperidine, a new type of basic side-chain recently developed (1), which seems to have the property of reducing toxicity without lowering the activity of 4-substituted quinolines as antimalarials.

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VITA

The author was born in Rochester, New York, on October 29, 1921. He attended the public schools of that city, graduating from Monroe High School in June, 1940. The following fall he entered the University of Rochester. He received a degree of B. S. in chemistry from that institution in August, 1943. On October 1st of that year he entered the graduate school of the University of Illinois, where he held a position as Special Research Assistant until February, 1946, employed under a contract recommended by the Office of Scientific Research and Development between the Committee on Medical Research and the University of Illinois. From that time to June, 1946, he held a fellowship granted by the Allied Chemical and Dye Corporation.

